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TITLE: The important role of the histopathologist in clinical trials: challenges and approaches to tackle them

RUNNING TITLE: Role of the histopathologist in clinical trials

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ABSTRACT:

High quality histopathology is essential for the success of clinical trials. Histopathologists have a detailed understanding of tumour biology and mechanisms of disease, as well as practical knowledge of optimal tissue handling and logistical service requirements for study delivery such as biomarker evaluation, tissue acquisition and turnaround times. As such, histopathologist input is essential through every stage of research and clinical trials from concept development and study design, through trial delivery, to analysis and dissemination of results. Patient recruitment to trials takes place across all healthcare settings meaning histopathologists make an invaluable contribution to clinical trials as part of their routine day to day work that often goes unrecognised. More complex evaluation of surgical specimens in the neoadjuvant setting and ever-expanding minimum datasets add to the workload of every histopathologist, not just academic pathologists in tertiary centres. This is occurring against a backdrop of increasing workload pressures and a worldwide shortage of histopathologists and biomedical scientists. Providing essential histopathology support for trials at grassroots level requires funding for adequate resources including histopathologist time, education and training, biomedical scientist and administrative support, and greater recognition of the contribution made by histopathology. This paper will discuss the many ways histopathologists are involved in clinical trials, the challenges faced in meeting the additional demands posed by trial participation, and potential ways to address this with a special emphasis on the UK model and the Cellular-Molecular Pathology Initiative (CM-Path).

KEY WORDS: Histopathology, clinical trials, resources, education

Introduction

High quality histopathology is a critical component of many clinical trials. Histopathologists have a detailed understanding of tumour biology and mechanisms of disease as well as practical knowledge of optimal tissue handling and the technical considerations behind testing protocols. As such histopathologist input is essential through every stage of research and clinical trials from concept development, through delivery to analysis and dissemination of results (figure 1/ supplementary table 1).

Histopathologist participation is key in ensuring correct patient selection. This incorporates traditional tumour classification by morphological subtyping, as well as assessment of biomarkers using immunohistochemistry and molecular techniques. Neoadjuvant therapy is increasingly used in trials, with the advantage of smaller, more cost-effective studies with pathological complete response (pCR) as a surrogate of long-term survival benefit providing earlier results[1-3]. Hence, in neoadjuvant trials it is the histopathologist that provides the primary trial outcome. Accurate assessment of response to therapy requires detailed macroscopy, thorough sampling and precise microscopic evaluation[4]. In both correctly identifying patients for trials and determining outcome measures, results must be reproducible requiring precise definitions and stringent quality assurance (QA) protocols.

In addition, new biomarkers identified by trials need to be incorporated into routine diagnostic practice in order for novel agents to become standard therapy. This requires standardised protocols for assessment, training in interpretation, ongoing QA to ensure equivalent results within and between centres, and provision of adequate resources and funding

Patients are recruited to trials in all healthcare settings meaning histopathologists make an invaluable contribution to clinical trials as part of their day to day work. More complex

evaluation of surgical specimens and ever-expanding minimum datasets add to the workload of every histopathologist, not just academic pathologists in tertiary centres. Providing essential histopathology support for trials at grassroots level requires funding for adequate resources including histopathologist time, education and training, biomedical scientist and administrative support, and greater recognition of the contribution made by pathology.

This paper will discuss the many ways histopathologists are involved in clinical trials and the challenges faced in meeting the additional demands posed by trial participation, and ways to address this with a special emphasis on the UK model.

Histopathologist role in trials

The roles of histopathologists in research include:

Research development/ generation

With their understanding of basic biology and the direct observation of morphological features under the microscope, histopathologists are well positioned to identify key questions and take the lead in initiating and leading clinical research as a Chief Investigator. This entails a significant time commitment, from procuring funding in today's highly competitive grant environment, access to staff and facilities to deliver the project, and analysis and dissemination of results, and is predominantly but not exclusively undertaken by individuals with dual clinical and academic appointments in larger centres. This is becoming an increasingly rare occurrence internationally due to dwindling numbers of academic pathologists.

More commonly, histopathologists make a significant contribution to trial design as part of a multidisciplinary team (collaborator/ co-investigator). Histopathologists provide unique clinical and analytical expertise that is vital in the initial development and design of clinical trials, and understand the practical elements of study delivery; service requirements in terms

of diagnostic pathways, biomarkers [selection, interpretation, limitations, QA and reproducibility], tissue access and real-world restrictions including turnaround times and logistics of sample acquisition. The histopathologist should be consulted across the entire development programme, including target and or biomarker validation, attending scientific advice meetings with regulatory authorities, writing the clinical trial protocol and study report, and ensuring that histopathology standards and the clinicopathological interpretation of the research data are conveyed consistently and in accordance with international and national standards (e.g. REMARK[5], International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH)[6], Royal College of Pathologists (RCPath)[7]). An understanding of these factors, and the associated financial costs, is crucial to designing a successful study. Central trial histopathologists also provide an essential link between the trial team and local histopathologists, without whose co-operation successful trial delivery is not possible.

Whilst pathologist representation is an intrinsic part of many co-operative clinical trial groups internationally (for example the National Cancer Research Institute (NCRI) in the U.K., GEICAM/ GEICO in Spain), unfortunately it is still the exception for pathologists to be involved early in the trial design process. The more typical scenario is being presented with a complete or near complete protocol with funding already determined. The Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) statement aims to improve the completeness and quality of clinical trial protocols and has been endorsed by international funders, regulators, industry and researchers[8]. Robust and consistent interpretative pathology is essential as a central pillar of patient selection and tissue-based endpoint assessment in clinical trials, but there are currently no cogent and formalised standards for pathological input into trial design and delivery. Through the UK National Cancer Research Institute Cellular Molecular Pathology Initiative and with the support of the SPIRIT group, the

SPIRIT-Path project is developing international, consensus-based, pathology-specific protocol guidance as an extension to the SPIRIT statement, and the protocol for the supporting literature search is available from the Centre for Open Science OSF registry [9,10]. Such guidelines will provide a mechanism for the appropriate involvement, recognition and funding of pathologists in clinical trials work.

Research delivery

Histopathology services are integral to the delivery of clinical trials, particularly those for oncological drug treatments. Site histopathologists provide the initial diagnosis to correctly determine eligibility. Tissue samples taken specifically for the trial must be carefully and consistently selected, embedded, processed and H&E slides cut and stained for histopathological assessment, e.g. to determine tumour content. Often diagnostic archive tissue is required to be released to a central laboratory. Archival cases must be identified, slides reviewed and appropriate blocks selected and retrieved, and the material securely delivered. In addition, histopathologists are key in the Biobanking pathway by collecting relevant fresh, frozen and fixed samples for various translational techniques including DNA/RNA extraction, cell culture, genetic testing or banking for future translational research. Histopathologists provide samples for Biobanks across the world facilitating international collaborations necessary for the global impact of translational research[11]. Histopathologists may be requested to analyse tissue samples for biomarker expression or assess treatment effect in tissues as an endpoint.

Examples of how pathology involvement is instrumental to clinical trial delivery are provided in table 1.

Solving the barriers to Histopathology Involvement

In the U.K., The Cellular Molecular Pathology Initiative (CM-Path) has been set up to support academic pathology and address barriers for trials and translational research. The clinical trials workstream has conducted several surveys of UK pathologists and identified the main barriers to participation in research as time constraints, lack of remuneration, and perceived lack of trial knowledge and skills. Feedback from pathologists in the U.S., Europe, Asia and Australia highlight similar issues across the globe. There is a universal lack of recognition of the additional workload brought by clinical trials in departmental and individual job planning. Depending on the nature of the trial (academic versus commercial sponsor) there may be some reimbursement for laboratory work such as block retrieval or performance of biomarkers, but this is often insufficient to cover the total costs involved, and excludes payment for pathologist activities such as slide review or biomarker scoring. In some countries, such as the U.S. and Australia, pathologist trial participation is further complicated by private health care systems.**Adequate staffing**

Clinical trials require the input of a diverse workforce including archivists, secretaries, and biomedical scientists as well as histopathologists. In many countries worldwide including the U.K., there is a current shortage of histopathologists and biomedical scientists[12]. A recent workforce report by the RCPath highlighted that 97% of UK laboratories are under staffed[13]. Due to this pressure delivery of essential diagnostic services and meeting clinical turnaround times are often prioritised over 'extras' such as clinical trials, which risks impeding the delivery of therapeutic improvements for patients. Departmental management must ensure clinical trial work can be adequately resourced and carried out in a timely manner, so patients do not miss out on trial opportunities.

There is great variation across histopathology departments, in the U.K. and globally, in terms of how clinical trial work is delivered, costed and funded. Some larger centres have tissue

banks with staff and resources specifically allocated to research including support of clinical trials. However, in the majority of departments, this additional workload must be absorbed by routine laboratory staff without compromising the delivery of basic diagnostic services. This needs to change, with dedicated time and resource set aside for consultant pathologists, histopathology trainees and biomedical scientists to contribute their expertise consistently into trials.

There are currently no recommendations for adequate staffing for research in the UK. RCPath Guidelines on staffing, and workload for histopathology departments state "*In departments with research programmes, there may be specific dissection and reporting protocols for research projects that take extra time compared with that for normal specimen handling. We recommend that the extra time taken is classified as research and that appropriate SPA time is allocated in the job plan*"[14]. Since the implementation of National Institute of Health Research Clinical Research Networks (NIHR CRN), every National Health Service (NHS) Trust is now active in research so every department may be called upon to undertake these activities. Pathology staff job descriptions should provide clarity with regard to responsibility and accountability for clinical trials. Ensuring the pathology workforce has both the capability and capacity to support this will be challenging. In parallel, there has been a decline in academic pathology staff. However, the CM-Path initiative, with the support of other stakeholders, is working on ways to reverse this trend and increase the recognition of research in pathologist training and continued professional development (CPD).

Funding sources

As described, a histopathologist will sometimes be formally named as an investigator on a trial and the research grant will have funding to cover their contributions. This section focuses on site histopathology departments being asked to contribute research delivery

activity in support of a trial or research study by, for example, scoring biomarkers, submitting tissue blocks and/or slides or completing pathology-based Case Report Forms (CRF). Many departments, sometimes due to lack of awareness or administrative support, complete these activities without seeking remuneration.

There have been increases in both the clinical trials requiring histopathology input and in the overall workload of histopathology departments; for example, at University College London Hospital (UCLH) there are currently over 150 trials set up that require histopathology input. The cellular pathology lab at UCLH is run by a private company and it has a very comprehensive system for costing trials and for ensuring that all laboratory work is paid for. All new trials requiring pathology input must be registered on a portal so laboratory and histopathology leads are aware of their existence. However, one major problem is pathologist time is not costed as the pathology consultants are employed by the NHS not the laboratory. Similarly, the Dana Farber Cancer Institute in Boston requires pathologist review of all clinical trials before granting Institutional Review Board approval. These examples highlight the importance of local pathologist consultation prior to initiation of trials with respect to availability of resources, budget implications, appropriateness of protocols, and the need for direct pathology input where this has not already been incorporated.

Hence, it is increasingly important that Pathology Departments understand how funding works for research, and ensure they receive their fair share of any funding that can be used to maintain and further develop trial capabilities. A detailed description of NHS research funding avenues is provided in Supporting Information.

A potential problem is the lack of recognition by those developing and funding clinical trials as to the contribution made by histopathology and the resources involved; specific funds for the provision of histopathology services will not be allocated if these are not highlighted

during trial design and identified in the grant application. Funding from the trial itself, via its research grant and/or commercial sponsor, should cover all pure research costs incurred by a histopathology department for that trial. Commercial trials are expected to cover all costs to the NHS for research, although in practice this often covers laboratory work such as section cutting or immunohistochemical tests but does not incorporate pathologist time. Non-commercial trials in the U.K., if they are on the NIHR CRN Portfolio, are eligible for NHS Support Costs funding provided via the local network.

Accurate billing for pathology services can be difficult as laboratory setups differ nationally and internationally, and it is hard to precisely quantify the contribution made across the department to clinical trials. Some histopathology departments have a standard list of research costings, including those to cover specific pathologist activities (Supplementary table 2). Appropriate funding is vital for provision of resources to improve clinical trial engagement, such as dedicated histopathologist time to oversee the clinical trials work and co-ordinate research opportunities for all staff.

Whilst adequate resources and funding are pivotal, other potential alternative methods to recognise pathologists' contribution include:

- Authorship/ acknowledgement on publications
- Certificate of participation/ appreciation from clinical trial investigators recognising the contribution of a pathologist to the trial
- Support for pathologists' applications to Clinical Excellence Awards or international equivalents
- CPD accreditation: recognising the tasks and time spent on slide review, block selection, biomarker assessment
- Mentorship: pairing up pathologists with varied expertise to enhance trial participation and sharing good practice.

Clinical Trials Expertise and Regulation

Histopathology staff providing support activity to a clinical trial must be adequately qualified, trained and experienced to assume clinical research responsibilities[15]. The research regulations, standards and guidelines that apply to pathology departments in the U.K. are reviewed in recent papers from CM-Path[16,17]. Clinical trials regulations and professional standards require staff to be trained commensurate with their roles and staff should be able to provide up-to-date training records and/or curriculum vitae. Whilst there is a lack of standardised training targeted at the needs of histopathologists, CM-Path and the RCPath in conjunction with organisations like the NIHR CRN are seeking to correct this via trials days and online resources. There is also a need for greater exposure to clinical trials as part of the histopathology training curriculum and more comprehensive CPD with respect to clinical trial development and delivery. In Europe, a joint ESP-EORTC fellowship program has been established to help young pathologists become active in trials and research[18]. A need for similar initiatives in other countries is recognised.

Through CM-Path activities so far, there has been increased recognition of the importance of considering histopathology requirements during clinical trial design and better representation of histopathologists on the relevant committees. Its subgroup, the Clinical Trials - Pathology Advisory Group (CT-PAG) includes expert academic pathologists of various disciplines who not only offer advice to clinical trial designers on all aspects of tissue collection and testing, but to histopathologists and trainees as to how they can become more involved (cmpath.ncri.org.uk).

Histopathologists may be unfamiliar with the regulatory requirements, which include the processes for approving clinical trials by competent authorities (e.g. by the MHRA in the

UK) or CE marking of in vitro diagnostic products in the context of personalised medicine by Notified Bodies. There are also inspections of facilities to ensure maintenance of the standards of Good Clinical Practice (GCP). GCP is particularly important for ensuring that the results of clinical trials are trustworthy and credible, and histopathologists involved in clinical research are often required to undertake additional specific training. It should be noted that regulatory standards and science continue to evolve, e.g. major amendments to the requirements for medical devices (including criteria for in vitro diagnostic approvals and the health institution exemption), and the soon to be implemented clinical trial regulation. Therefore, knowledge of the regulatory requirements requires regular review and implementation of all the relevant documents and standards. In areas of uncertainty scientific advice should be sought from local regulatory authorities, particularly if a development plan deviates from the recommendations found in published regulatory guidelines or if these documents are considered not to have sufficient detail, where new technologies are moving fast from the bench to the clinic (e.g. digital pathology with artificial intelligence algorithms[19]). These interactions require time and resource and are critical for the successful and efficient development of new drugs and diagnostics in the personalised medicine era.

Summary and conclusion

Pathology is key to clinical trials success and histopathologists actively contribute to trials as part of their routine work. Histopathology input is essential at each stage of trial design and delivery. Adequate resources and funding are urgently needed to enable greater engagement by pathologists in clinical trials. The SPIRIT-Path project is developing international, consensus-based, pathology-specific protocol guidance. CM Path is working closely with the RCPath and NCRI in the UK to find practical solutions, and to educate consultant histopathologists and trainees in the design and delivery of clinical trials so they can reap the

personal and professional rewards gained by participation in clinical trials and subsequent improvements in delivery of patient care.

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SUPPORTING INFORMATION

Supplementary Table 1: Levels of involvement of pathologists and their potential contribution at each stage of the clinical trial process

Supplementary Table 2: Example of costings for histopathology work for clinical trials

Supporting document 1: Detailed description of NHS funding avenues for histopathology work done in support of clinical trials

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Figure 1: Contribution of histopathologists at each stage of the clinical trial process

Table 1: Examples of the role of histopathology in clinical trials including specific issues